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On June 10, 2002

TOWNSEND and TOWNSEND and CREW LLP

By: Joy M. Marshall

PATENT
Attorney Docket No.: 018512-002210US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

JEGLA, Timothy James

Application No.: 09/548,933

Filed: April 13, 2000

For: HUMAN HAC3

Examiner: Chernyshev, Olga

Art Unit: 1646

DECLARATION UNDER 37 C.F.R § 1.132
OF DR. NEIL CASTLE

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Neil Castle, Ph.D., being duly warned that willful false statements and the like are punishable by fine or imprisonment or both (18 U.S.C. § 1001), and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true, and statements made on information or belief are believed to be true and correct.

2. I received a B.S. in Pharmacology from the University College of London in 1983. I received a Ph.D. in 1987 in Pharmacology from the University College of London. From 1987 to 1990, I was a postdoctoral fellow at Harvard University. From 1990-1995, I was faculty at Harvard Medical School in the Department of Anesthesia. A copy of my curriculum vitae is attached hereto as Exhibit A.

3. I have worked in the field of ion channel discovery at ICAgen, Inc. since 1995. Currently, I am Associate Director of Biology at ICAgen, Inc.

4. The present invention claims isolated nucleic acids of a Hac3 cation channel which plays a key role in promoting neuronal excitability and is widely expressed in the central nervous system ("CNS").

5. I have read and am familiar with the contents of the patent application. In addition, I have read the Office Action, mailed December 10, 2001, received in the present case. It is my understanding that the Examiner believes that the present invention is supported by neither a specific, substantial, and credible asserted utility nor a well established utility as required by the United States Patent Laws. I respectfully disagree. This declaration is provided to demonstrate that the identification of the Hac3 cation channel has utility.

6. The Hac3 channel modulates cell excitability in the CNS. The identification of the Hac3 channel has utility, therefore, because it makes possible the routine identification of agonists and antagonists of the Hac3 channel, e.g., for treatment

of CNS diseases related to cell excitability. Modulating cell excitability is useful because many CNS diseases, including epilepsy and migraines, are characterized by hyperexcitability of the cell. Because the present application provides nucleic acid sequences encoding a Hac3 channel and methods of activating a Hac3 channel, the skilled practitioner can routinely identify agonists or antagonists of a Hac3 channel useful for modulating neuronal excitability in the cell and in controlling CNS diseases related to CNS excitability, e.g., epilepsy and migraines.

7. Hac3 encodes a hyperpolarization-activated cation channel. Hyperpolarized activated cation channels are known to be widely expressed in the central nervous system. Figure 2 of the present application demonstrates that Hac3 is expressed primarily in the CNS. It is widely known that hyperpolarization activated cation channels play a key role in promoting neuronal excitability (see enclosed reference by Pape, *Ann Rev Physiol*, 58:299-327, 1996). Hyperpolarization-gated cation channels promote neuronal and therefore cell excitability by depolarizing resting potential (so that even small excitations can cause action potential firing) and by directly causing excitatory rebound potentials in response to hyperpolarization.

8. Because of the functional properties and distribution of Hac3, one of skill in the art would readily recognize Hac3 as a useful target for the treatment of diseases and conditions caused by altered neuronal or cell excitability. For example, one of skill in the art would expect blockers of Hac3 to decrease overall CNS activity. Thus, blockers of Hac3 channels have utility for the treatment of diseases of hyperexcitability, such as epilepsy and migraine. Treating diseases related to cell excitability by targeting ion channels is well known in the art. For example, many currently marketed epilepsy drugs control cell excitability by targeting excitatory ion channels with similarly broad distributions in the CNS. Blockers of Hac3 channels,

therefore, have utility for (1) modulation of cell excitability and (2) the treatment of diseases of hyperexcitability, such as epilepsy and migraine.

9. It is well known in the art that once an ion channel has been identified, agonists or antagonists of the ion channels can be routinely identified using the coding sequence of the ion channel gene and a method for activation of the channel. The present application provides sequences encoding a Hac3 channel. The present application also provides methods for activating a Hac3 channel. As provided in the specification, the Hac3 channel is activated by changes in voltage. Hac3 currents can be elicited by the application of voltage to cells expressing Hac3. Agonists and antagonists of Hac3 can routinely be identified by applying compounds to Hac3-expressing cells while applying voltage to the cells expressing Hac3 and measuring the effect on the magnitude of the Hac3 current. The blockage of the Hac3 current by cesium shown in figure 4 provides a direct example of the identification of an antagonist of the Hac3 channel.

10. There are known instances where modulation of an ion channel is useful for treating a specific disease even though the channel itself may not cause disease. For example, hypertension can be caused by a variety of illnesses such as renal disease and diabetes. Among the treatment strategies for hypertension is the use of drugs such as calcium channel blockers to relax the vasculature. Relaxing the vasculature to reduce blood pressure is useful and effective, even if the original cause of the hypertension is unrelated to vascular tone. Similarly, it is perfectly reasonable to expect that the targeting of Hac3, a hyperpolarization-activated cation channel widely expressed in the CNS, is an appropriate strategy for suppressing hyperexcitability in diseases such as epilepsy without respect to the original cause of the condition. Thus the information provided in the above-referenced patent application is sufficient to establish the utility of Hac3.

11. In view of the foregoing, it is my scientific opinion that one of skill in the art, at the time the application was filed, would recognize the real world utility of the nucleic acids of the present invention.

Date: 5/31/02 By: _____

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Employment:

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Associate Director of Biology (May 2001- present)

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Principle Scientist - Head Of New Lead Discovery: (May 2000-May 2002)

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Assistant Director of Biology: (June 1998 – February 1999)
Chief Scientist (March 1996 – May 1998)
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Harvard Medical School, Boston, Massachusetts, USA
Brigham and Women's Hospital, Department of Anesthesia Research Laboratories

Assistant Professor (1991 - 1995)

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Education:

1983 B.Sc. University College London (Pharmacology)
1987 Ph.D. University College London (Pharmacology)

Posdoctoral Training:

1987-1990 Postdoctoral Fellow, Harvard Medical School, Brigham and Women's Hospital, Boston

Hospital Appointments:

1987-1989 Associate Physiologist, Brigham and Women's Hospital (Anesthesia)

Memberships, Offices and Committee Assignments in Professional Societies:

Biophysical Society

Research Funding Information:

1989-1990 American Heart Association/ Postdoctoral Fellowship PI
"Effects of anti-arrhythmic agents on potassium currents in mammalian ventricular muscle."

1991-1992 NIH/Biomedical Research Support Grant PI
"Are ATP-sensitive K^+ channels targets for intravenous general anesthetic agents?"

1993-1994 Cambridge Neuroscience Inc. PI
"Actions of anti-ischemic agents on cardiac sodium channels"

Training Responsibilities:

Postdoctoral Advisor for:

1992 - 1995 Dr. Mara Slawsky
1993 - 1995 Dr. Gil Gross

Faculty Member of Department of Pediactric Cardiology Postdoctoral Training Program at Childrens Hospital, Boston

Professional Activities:

Editorial services for:

Science, Circulation Research, Cardiovascular Research, British Journal of Pharmacology, American Journal of Physiology, Anesthesiology, Journal of Neuroscience, Neuroscience Letters, Toxicon, Journal of Membrane Biology, Biophysical Journal

ad hoc reviewer for Veterans Administration Merit Review Grant Committee (1993)

External reviewer for tenure evaluation at Department of Pharmacology, Columbia University, New York (1994)

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